

Remarks

Claims 11-18 and 20-22 are pending in the subject application. Applicants acknowledge that claims 13, 14, 17 and 18 have been withdrawn from further consideration as being drawn to a non-elected invention. By this Amendment, Applicants have canceled claims 13-18, amended claims 11, 12 and 20-22, and added new claims 23-26. Support for the amendments and new claims can be found throughout the subject specification and in the claims as originally filed (see, for example, page 3, lines 1-5). Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 11, 12, and 20-26 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

The Examiner has indicated that the title of the invention is not descriptive and that a new title is required that is clearly indicative of the invention to which the claims are directed. Applicants have amended the title of the invention to "CC-Chemokine CCL5/RANTES Mutant(s) Against Liver Diseases" which more clearly indicates the claims to which the invention is directed. Accordingly, reconsideration and withdrawal of this objection is respectfully requested.

The claims are objected to because of informalities for the use of the acronyms "GAG" and "CC-chemokine" without first defining what they represent. In regard to "GAG", Applicants have indicated that GAG is the acronym for "glycosaminoglycan". For the term "CC-chemokine", Applicants respectfully assert that this is not an acronym but art recognized standard nomenclature for a class of chemokines, as explained in the "Background of the Invention" section on pages 2-4 of the subject application. Finally, the acronym "RANTES" has been defined according to its art recognized meaning (see attached printout from the Online Mendelian Inheritance in Man database). Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claims 11, 12, 15, 16 and 20-22 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully assert that the claims as filed are definite. However, in view of the amendments made to the claims, it is respectfully submitted that this rejection is now moot. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 11, 12, 15, 16 and 20-22 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office Action indicates that the specification does not describe the common attributes or characteristics that identify members of the genus. Applicants respectfully assert that there is adequate written description in the subject specification to convey to the ordinarily skilled artisan that they had possession of the claimed invention. Applicants traverse.

As the Patent Office is aware, “the written description requirement can be met by ‘showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.’” See *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1324, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002). Additionally, the descriptive text needed to meet the written description requirement varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence and the law must be applied to each invention in view of the state of relevant knowledge and the application of the law will vary with differences in the state of knowledge in the field and differences in the predictability of the science. See *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 U.S.P.Q.2d 1078, 1084 (Fed. Cir. 2005).

In the case of the claimed invention, the claims were directed to the reduction of ALT levels in a subject comprising the administration of a CC-chemokine that has reduced GAG-binding activity. The CC-chemokine could be CCL3, CCL4 or CCL5. As indicated in the as-filed specification CC-chemokines having reduced GAG-binding activity are known in the art, the domains/amino acids associated with such reduced GAG-binding are also known and methods of substituting (*e.g.*, conservatively or non-conservatively) amino acid residues known to be associated with reduced GAG-binding area with other amino acids are also known (see specification at page 5, line 15 through page 7, line 5). As noted by the Court of Appeals for the Federal Circuit, there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure (see *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 U.S.P.Q.2d 1001 (Fed. Cir. 2006)). Thus, it is clear that the claimed triple 40’s

CCL5 mutant chemokines clearly comply with the written description requirement and reconsideration and withdrawal of the rejection is respectfully requested.

Claims 11, 12, 15, 16 and 20-22 are rejected under 35 U.S.C. § 112, first paragraph, as nonenabled by the subject specification. The Office Action acknowledges that the specification is enabled for a method of reducing serum alanine amino transferase (ATL) in a subject with hepatitis comprising the administration of the CCL5/RANTES mutant triple 40's of SEQ ID NO: 1, but is not enabled for a method of treatment of liver fibrotic inflammatory and/or liver autoimmune diseases comprising the administration of an effective amount of any CC-chemokine mutant having reduced GAG-binding activity wherein the CC-chemokine is CCL5/RANTES. Applicants respectfully assert that the claims are enabled by the subject specification.

Enablement is a legal determination of whether a patent enables one skilled in the art to make and use the claimed invention (*Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 960, 220 U.S.P.Q. 592, 599 (Fed. Cir. 1983)) and is not precluded even if some experimentation is necessary. *Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 U.S.P.Q. 409, 413 (Fed. Cir. 1984); *W.L. Gore and Associates v. Garlock, Inc.*, 721 F.2d 1540, 1556, 220 U.S.P.Q. 303, 315 (Fed. Cir. 1983). Applicants also submit that nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. Additionally, the Patent and Trademark Office Board of Patent Appeals and Interferences has stated: "The test [for enablement] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed". *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (1982); *see also Ex parte Erlich* 3 U.S.P.Q.2d 1011 (B.P.A.I. 1982) (observing that although a method might be "tedious and laborious," such experimentation is nevertheless "routine" defining "routine" experiments as those which use known methods in combination with the variables taught in the patent to achieve the expected, specific, patented result).

In the case of the instantly claimed invention, it is respectfully submitted that the claims comply with the enablement requirement of section 112. Applicants note that the Office Action

acknowledges that triple 40's and triple 50's RANTES mutants are known as are the residues associated with reduced GAG-binding activity (Office Action at page 11). The Office Action then argues that because triple 40's mutants containing amino acid residues other than alanine are not discussed in the prior art and concludes that undue experimentation would be required to practice the claimed invention. As noted above, compliance with the enablement requirement is not precluded even if some experimentation is necessary. Further, a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. In this respect, it is submitted that the as-filed specification provides adequate guidance as to any experimentation that should proceed in order to identify 40's triple mutants of CCL5 containing amino acid residues other than alanine and that exhibit reduced GAG-binding activity. Indeed, the as-filed specification provides teachings as to which residues should be changed in accordance with the teachings of the specification as well as those amino acids that can be inserted into those amino acid residue positions (see specification at pages 6-7). Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Frank C. Eisenschenk". The signature is fluid and cursive, with a long horizontal stroke at the end.

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Attachment: Online Mendelian Inheritance in Man database

Select 187011

☐ 1:\*187011**CHEMOKINE, CC MOTIF, LIGAND 5; CCL5*****Alternative titles; symbols*****SMALL INDUCIBLE CYTOKINE A5; SCYA5****REGULATED UPON ACTIVATION, NORMALLY T-EXPRESSED, AND PRESUMABLY SECRETED;  
RANTES****T CELL-SPECIFIC RANTES****T CELL-SPECIFIC PROTEIN p228; TCP228****TABLE OF CONTENTS**

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Gene map locus [17q11.2-q12](#)**TEXT****CLONING**


Using a human cDNA library that was enriched by subtractive hybridization for sequences expressed by T lymphocytes but not B lymphocytes, [Schall et al. \(1988\)](#) isolated a gene (D17S136E), which they designated RANTES, that encodes a novel T cell-specific molecule. (RANTES is an acronym for 'Regulated upon Activation, Normally T-Expressed, and presumably Secreted.') The gene product was predicted to be a 10-kD protein which, after cleavage of the signal peptide, could be expected to be approximately 8 kD. Of the 68 residues, 4 are cysteine and there are no sites for N-linked glycosylation. Significant homology (30 to 70%) was found between the RANTES sequence and several other T-cell genes, suggesting that they constitute a family of small, secreted T-cell molecules. 💡


[Schall et al. \(1988\)](#) found that RANTES, also designated p228 (TCP228), was expressed in 10 functional T-cell lines, but not in 8 hematopoietic tumor lines or in 6 T-cell tumor lines. Its expression was increased more than 10-fold in peripheral blood lymphocytes 3 to 5 days following mitogenic or antigenic stimulation. 💡


**GENE FUNCTION**

CD8-positive T lymphocytes are involved in the control of human immunodeficiency virus (HIV) infection in vivo


(see 609423). Cocchi et al. (1995) demonstrated that the chemokines RANTES, MIP-1-alpha (182283), and MIP-1 beta (182284) are the major HIV-suppressive factors produced by CD8-positive T cells. HIV-suppressive factor activity produced by either immortalized or primary CD8-positive T cells was completely blocked by a combination of neutralizing antibodies against these 3 cytokines. On the other hand, recombinant forms of the 3 human cytokines induced a dose-dependent inhibition of different strains of HIV-1, HIV-2, and simian immunodeficiency virus (SIV). Cocchi et al. (1995) speculated that chemokine-mediated control of HIV may occur either directly, through their inherent anti-lentiviral activity, or indirectly, through their ability to chemoattract T cells and monocytes to the proximity of the infection foci. However, this latter mechanism may also have the opposite effect of providing new, uninfected targets for HIV infection. The authors noted that the findings may be relevant for the prevention and therapy of AIDS. 


Arenzana-Seisdedos et al. (1996) investigated a derivative of RANTES as a possible therapeutic agent for inhibition of HIV infection. The derivative, called RANTES(9-68), lacks the first 8 N-terminal amino acids and has no chemotactic or leukocyte-activating properties. RANTES(9-68) was a potent receptor antagonist and inhibited infection of macrophage-tropic HIV. The anti-HIV activity was somewhat lower than that of RANTES itself, which correlated with its lower affinity for CC chemokine receptors. Arenzana-Seisdedos et al. (1996) found that the anti-HIV activity of RANTES and RANTES(9-68) showed some variability depending on the donor cells. The authors concluded that structural modification of a chemokine can yield variants lacking activation properties but retaining both high-affinity for chemokine receptors and the ability to block HIV infection. 

Using astrocytes obtained from 5- to 10-week-old fetal forebrains and in situ hybridization and immunohistochemical analyses, Bakhiet et al. (2001) showed that expression of RANTES mRNA and protein, but not of other chemokines, increases with age. Responses to RANTES in cultured astrocytes differed with age. Stimulation of 5-week-old astrocytes enhanced their proliferation but not their survival, whereas stimulation of 10-week-old cells prolonged their survival but diminished their ability to proliferate. The RANTES receptors, CCR1 (601159), CCR3 (601268), and CCR5, were all found to be expressed on astrocytes in vivo. Immunohistochemical and in situ hybridization analysis showed that cells expressing CCR5 do not express RANTES mRNA, while cells lacking CCR5 do express RANTES mRNA, suggesting a paracrine mode of action. Using astrocytes from wildtype and Ccr5 -/- mice at embryonic day 7, which are equivalent to 10-week-old human cells, Bakhiet et al. (2001) demonstrated that RANTES inhibited proliferation and prolonged survival of wildtype cells but had no effect on the Ccr5 -/- cells. In response to RANTES stimulation, 5- and 10-week-old human astrocytes enhanced their production of gamma-interferon (IFNG; 147570), but only the older cells expressed IFNG receptor (IFNGR; see 107470). Blockade of IFNGR reversed RANTES inhibition of proliferation and promotion of survival. Immunoblot analysis showed that RANTES stimulation of 5-week-old cells rapidly increased tyrosine kinase activity and protein phosphorylation. Immunofluorescence microscopy revealed that RANTES stimulation of 5- or 10-week-old astrocytes induced the translocation of STAT1 (600555) from the cytoplasm to the nucleus. Bakhiet et al. (2001) concluded that RANTES regulates the growth and survival of first-trimester forebrain astrocytes. Furthermore, they suggested that chemokines are not only mediators of inflammation, but are also significant regulators of differentiation in development. 


Pritts et al. (2002) investigated the effect of PPAR-gamma ligands upon transcription and translation of RANTES in human endometrial stromal cells. Three putative PPAR response elements (PPREs) were found in the human RANTES promoter. In cells transfected both with RANTES promoter vectors containing 958 bp and 3 PPREs, the addition of 2 PPAR-gamma ligands inhibited promoter activity by 60% (P less than 0.01) and 48% (P less than 0.02), respectively. Truncation of the gene promoter to delete all putative PPREs abrogated the ligand-induced inhibition. Stromal cells showed a 40% decrease in RANTES protein secretion when treated with a PPAR-gamma ligand (P less than 0.01). The authors concluded that use of PPAR-gamma ligands to reduce chemokine production and inflammation may be a productive strategy for future therapy of endometrial disorders, such as endometriosis. 

Apolinario et al. (2002) found that CCL5 expression was low in normal liver, but it was significantly enhanced after hepatitis C virus (HCV; see 609532) infection, particularly in areas with greatest lymphocytic infiltration.


Once virus-infected cells are eliminated by cytotoxic lymphocytes, removal of these dead cells requires macrophage clearance without the macrophages being killed by virus. [Tyner et al. \(2005\)](#) showed that Ccl5-deficient mice had delayed viral clearance, excessive airway inflammation, and respiratory death after infection with either murine parainfluenza or human influenza viruses. CCL5 was required to hold apoptosis and mitochondrial dysfunction in check in virus-infected mouse macrophages in vivo and mouse and human macrophages ex vivo, and the protective effect of CCL5 required activation of CCR5 ([601373](#)) and the downstream ERK1 (MAPK3; [601795](#))/ERK2 (MAPK1; [176948](#)) and AKT ([164730](#)) signaling pathways. 

[Karnoub et al. \(2007\)](#) demonstrated that bone marrow-derived mesenchymal stem cells, when mixed with otherwise weakly metastatic human breast carcinoma cells, cause the cancer cells to increase their metastatic potency greatly when this cell mixture is introduced into a subcutaneous site and allowed to form a tumor xenograft. The breast cancer cells stimulate de novo secretion of the chemokine CCL5 from mesenchymal stem cells, which then acts in paracrine fashion on the cancer cells to enhance their motility, invasion, and metastasis. This enhanced metastatic ability is reversible and is dependent on CCL5 signaling through the chemokine receptor CCR5. [Karnoub et al. \(2007\)](#) concluded that the tumor microenvironment facilitates metastatic spread by eliciting reversible changes in the phenotype of cancer cells. 

## MAPPING

By analysis of somatic cell hybrids and by in situ hybridization using the cDNA probe, [Donlon et al. \(1990\)](#) assigned the RANTES locus to 17q11.2-q12. A secondary hybridization peak was noted in the region 5q31-q34, which may represent the location of other members of the gene family. The region on chromosome 5 overlaps with the location of an extended linked cluster of growth factor and receptor genes, some of which may be coregulated with members of the RANTES gene family. 


## MOLECULAR GENETICS

RANTES is one of the natural ligands for the chemokine receptor CCR5 and potently suppresses in vitro replication of the R5 strains of HIV-1, which use CCR5 as a coreceptor. Previous studies showing that peripheral blood mononuclear cells or CD4<sup>+</sup> lymphocytes obtained from different individuals have wide variations in their ability to secrete RANTES prompted [Liu et al. \(1999\)](#) to analyze the upstream noncoding region of the RANTES gene, which contains cis-acting elements involved in RANTES promoter activity, in 272 HIV-1-infected and 193 non-HIV-1-infected individuals in Japan. They found 2 polymorphic positions, 1 of which was associated with reduced CD4<sup>+</sup> lymphocyte depletion rates during untreated periods in HIV-1-infected individuals. This -28G mutation of the RANTES gene ([187011.0001](#)) occurred at an allele frequency of approximately 17% in the non-HIV-1-infected Japanese population and exerted no influence on the incidence of HIV-1 infection. Functional analyses of RANTES promoter activity indicated that the -28G mutation increases transcription of the RANTES gene. Taken together, these data suggested that the -28G mutation increases RANTES expression in HIV-1-infected individuals and thus delays the progression of the HIV-1 disease. 


[An et al. \(2002\)](#) tested the influence of 4 RANTES SNPs and their haplotypes on HIV-1 infection and AIDS progression in 5 AIDS cohorts. Three SNPs in the RANTES gene region on chromosome 17 (403A in the promoter In1.1C in the first intron, and 3-prime 222C in the 3-prime UTR) were associated with increased frequency of HIV-1 infection. The In1.1C SNP allele is nested within an intronic regulatory sequence element ([168923T/C](#); [187011.0002](#)) that exhibits differential allele binding to nuclear proteins and a downregulation of gene transcription. The In1.1C allele, or haplotypes that include In1.1C, display a strong dominant association with rapid progression to AIDS among HIV-1-infected individuals in African American, European American, and combined cohorts. The principal RANTES SNP genetic influence on AIDS progression derives from the downregulating RANTES In1.1C allele, although linkage disequilibrium with adjoining RANTES SNPs, including a weaker upregulating RANTES promoter allele (-28G; [187011.0001](#)), can modify the observed epidemiologic patterns. The In1.1C-bearing genotypes accounted for 37% of the attributable risk for rapid progression among African Americans and may also be an important influence on AIDS progression in Africa. The diminished transcription of RANTES afforded by the In1.1C regulatory allele is consistent with increased HIV-1 spread in vivo, leading to accelerated progression to



AIDS. **ALLELIC VARIANTS**  
**(selected examples)****.0001 HUMAN IMMUNODEFICIENCY VIRUS TYPE 1, DELAYED DISEASE PROGRESSION WITH INFECTION BY [SCYA5, -28C-G]**

In a large Japanese cohort of HIV-1-infected and non-HIV-1-infected individuals, [Liu et al. \(1999\)](#) identified a C-to-G transversion at position -28 in the promoter of the SCYA5 gene, also referred to as the RANTES gene. The -28C allele had a frequency of approximately 17% in the Japanese population and appeared to have no influence on the incidence of HIV-1 infection. However, functional analyses indicated that the -28G mutation increased transcription of the RANTES gene. [Liu et al. \(1999\)](#) suggested that the -28G mutation increases RANTES expression in HIV-1-infected individuals and thus delays the progression of the HIV-1 disease (see [609423](#)). They showed that the -28C mutation is associated with reduced rates of depletion of CD4+ lymphocytes in HIV-1-infected individuals, thus confirming that this polymorphism delays HIV-1 disease progression. 

**.0002 HUMAN IMMUNODEFICIENCY VIRUS TYPE 1, RAPID DISEASE PROGRESSION WITH INFECTION BY [SCYA5, 168923, T/C ]**

Among 7 SNPs within the RANTES gene investigated by [An et al. \(2002\)](#), one was the intronic RANTES regulatory element, In1.1T/C (168923T/C). They found that In1.1C-bearing genotypes accounted for 37% of the attributable risk for rapid progression to AIDS (see [609423](#)) among African Americans. Because 36% of African Americans carry the In1.1C allele, it is likely that In1.1C may have a significant impact on the AIDS epidemic in sub-Saharan Africa. 

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